RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 78-84 and 86-94 were pending at the time the Final Office Action was mailed. Claims 78, 80-84, 86-87 and 89-93 are amended herein, and claims 79 and 88 have been canceled. Therefore, claims 78, 80-84, 86-87 and 89-94 are currently pending.

Claim 78 was amended to incorporate the limitation of claim 79, and claims depending from claim 78 were amended accordingly. Claim 87 was amended to incorporate the limitation of claim 88, and claims depending from claim 87 were amended accordingly. Claims 78, 80, 86-87 and 89 were also amended to reflect the election made in Applicant's response to the Restriction Requirement issued in this case. No new matter is introduced by these amendments.

B. Priority

The amendment to the specification to recite the priority information of the present application is objected to for the alleged introduction of new matter. Applicants respectfully traverse, but note that the priority paragraph has been amended herein to address the Examiner's concern.

The characterization of the relationship of the present application to U.S. Patent Application Serial No. 09/662,270 has also been corrected.

Removal of the objections is respectfully requested.

C. Specification

The specification is objected to for improper demarcation of trademarks. In response, the specification has been amended to clearly define trademarks that are used in accordance with MPEP § 608.01(v).

The specification is further objected to for inclusion of embedded hyperlinks. In response, embedded hyperlinks have been removed where appropriate. The specification no longer includes browser-executable code: thus, the specification complies with MPEP § 608.01(p).

In view of the foregoing amendments to the specification, it is respectfully requested that all objections to the specification be reconsidered and removed.

D. Claim Objection

The Examiner objects to the pending claims for improperly reflecting Applicant's election in response to the Restriction Requirement issued in this case. The claims have been amended in this regard and thus, Applicant respectfully requests reconsideration and removal of the objection.

E. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

1. Written Description

The Examiner rejects claims 78-82, 86-91 and 94 as failing to comply with the written description requirement stipulated in 35 U.S.C. §112, first paragraph. The Examiner contends that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner states that the genus of "agents" recited in the claims includes structurally and functionally disparate molecules

including, for example, naked antibodies, that specifically bind to a polypeptide and inhibit its activity or function, such that treatment of cancer cells with the antibody provides therapeutic benefit. The Examiner also contends that there is no language in the specification that adequately describes the genus of agents that bind a polypeptide of the present invention and inhibit its activity or function, so as to provide therapeutic benefit. To support this contention, the Examiner discusses the alleged lack of description regarding the activities of the polypeptides of the present invention, such that agents of the present invention could not inhibit these unknown activities. Applicant respectfully traverses this rejection.

As an initial point, Applicant notes that the contents of claim 79 have been incorporated into claim 78, and the contents of claim 88 have been incorporated into claim 87. As such, each pending independent claim recites, in part, "an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO:83 or SEQ ID NO:85, or a fragment thereof." These claims therefore are directed to antibodies that bind to certain peptides and/or polypeptides.

The Written Description Guidelines in the MPEP ("Guidelines") state the following:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

§ 2163 (internal citations omitted). As the following evidence shows, the specification complies with the written description requirement as set forth by these Guidelines regarding the claimed genus of antibodies that bind to a peptide or polypeptide encoded by SEQ ID NO:83 or SEQ ID NO:85, or a fragment thereof.

a. A Representative Number of Species of Antibodies Are Adequately Described

The specification describes a representative number of species of antibodies. For example, the specification provides examples of agents that bind to the polypeptides of the invention. Described in the specification is an antibody that was made to UC 28 (encoded by the nucleotide sequence of SEQ ID NOs: 3, 83 and 85). On page 117, lines 4 through 12 state:

> A first generation polyclonal antibody has been produced in rabbits using a KLH conjugated synthetic peptide (21 amino acids). The peptide, of sequence listed below, was chosen for antigenicity by a computer software program (DNASTAR™, Madison, WI).
>
> RKKEKVKRSQKATEFIDYSIE SEQ ID NO:56
>
> The synthetic peptide was conjugated to KLH by standard techniques and injected into two rabbits, with bleeding started at ten weeks. The antibody was peptide affinity purified and then tested in prostate cancer cell lines, and breast and prostate cancer tissue, confirming the localization of the UC 28 protein to epithelial cells, mainly on the cell membrane.

Applicant is prepared to deposit this antibody if this is deemed necessary to satisfy the written description requirement. Moreover, the Examiner has stated that antibodies conjugated to a radionuclide or a chemotherapeutic agent are adequately described by the specification. Action, page 10. In addition, monoclonal antibodies are discussed in the specification. *See, e.g.*, page 39, line 7 through page 44, line 28. Antibodies that are specific for particular cancer markers are also described. *See, e.g.*, page 11, lines 6-17. Thus, the specification describes an adequate number of representative species of the claimed genus of antibodies.

b. Functional Characteristics of the Claimed Antibodies Are Adequately Described

The present claims recite an "an effective amount of an antibody that binds to a peptide or polypeptide". Thus, the claimed antibodies possess the functional feature of binding to particular peptides or polypeptides. The Examiner admits as much by stating that the previously claimed

agents possess a "common ability to bind to the polypeptide encoded by the nucleotide sequences set forth as SEQ ID NO: 83 or SEQ ID NO: 85." Action, page 9. As such, at least one functional feature characteristic of the claimed genus has been adequately set forth in the specification.

c. Other Identifying Characteristics of the Claimed Genus of Antibodies Are Adequately Described

In addition to the exemplary species and functions of the claimed genus of antibodies, other relevant, identifying features of this genus are also set forth in the specification. For example, antibodies of the presently claimed invention may be used for diagnostic purposes. *See, e.g.*, specification at page 13, lines 11-17. The antibodies may be used to detect certain encoded peptides and proteins. *See, e.g.*, specification at page 45, lines 8-10.

d. Conclusion

The variety of types of antibodies described in the specification, in combination with their common ability to bind to SEQ ID NOs: 83 and 85 and the descriptions of other characteristics of this genus, demonstrate that the inventors were in possession of the claimed genus at the time the application was filed. Applicant therefore respectfully requests that the written description rejection be withdrawn.

2. Enablement

The Examiner rejects claims 78-94 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses.

The general standard for enablement under § 112, first paragraph, has been addressed in the case law repeatedly. For example, in *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993), the court stated that an enabling specification teaches those skilled in the art how to make and use the claimed invention in its full scope without "undue experimentation." 999 F.2d at 1560. It is well-settled patent law that the first paragraph of § 112 requires nothing more than objective

enablement. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). This objective enablement may be provided through broad terminology or illustrative examples. *Id.* As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). As will be shown, the present specification enables the claimed invention.

Once again, Applicant initially notes that the pending independent claims recite, in part, "an antibody that binds to a peptide or polypeptide encoded by SEQ ID NO:83 or SEQ ID NO:85, or a fragment thereof." These claims therefore are directed to antibodies that bind to certain peptides and/or polypeptides.

a. The Examiner's Arguments Relying On All Agents As Inhibitors Cannot Support an Enablement Rejection

In one aspect, the Examiner relies on the argument that the genus of claimed agents includes inhibitors, but that the function or activity of the claimed sequences is unknown—thus, the Examiner continues, a skilled artisan would have to perform undue experimentation to first determine such function or activity, then determine if that function or activity is related to cancer, and then design or discover an inhibitor of that function or activity. However, the term "inhibits" does not appear in the present claims, but only antibodies that "bind to" peptides and/or polypeptides encoded by the claimed sequences. Because the present claims do not require that the antibodies act as inhibitors, the Examiner's argument cannot be used to support an enablement rejection. Furthermore, and without conceding that any antibodies of the present invention are not enabled, "It is not a function of the claims to specifically exclude either possible inoperative substances...." *In re Dinh-Nguyen*, 492 F.2d 856 (CCPA 1974); *see also In*

re Hradcovsky, 214 USPQ 554 (PTO Bd. App. 1982); *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 588 F.Supp. 1455 (Tex. 1983).

As discussed above, the specification provides an example of a polyclonal antibody that binds to a polypeptide (UC 28) encoded by a nucleotide sequence (SEQ ID NOs: 3, 83 and 85) of the present invention. Page 117, lines 4-12. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Furthermore, failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. § 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 954 (1987).

Moreover, effective targeting of cancer cells with an antibody that binds to a peptide or polypeptide of the invention does not require determining the function or activity of the peptide or polypeptide, or whether the function of the peptide or polypeptide correlates with the onset of cancer, or the discovery of an inhibitor of that function activity. The Examiner does not assert that antibodies that *bind to* peptides or polypeptides of the present invention are not enabled. As such, the present claims are enabled.

b. The Specification Does Not Fail to Teach That UC 28 Is Expressed on the Membrane of Cancer Cells

In another aspect, the Examiner asserts that because the specification fails to teach whether the polypeptide encoded by SEQ ID NOs: 3, 83 and 85, designated therein as UC 28, is expressed at the surface of cells, the specification therefore fails to teach whether any antibody or other inhibitor can specifically bind to and exert any inhibitory effect on those cells. Instead, the

Examiner asserts that An *et al.* (*Cancer Res.* 60:7014-7020 (2000)) provides factual evidence that UC 28 (called "UROC 28" in An *et al.*) is not expressed at the surface of cells.

In response, Applicant notes that studies described in the specification on page 117, lines 10-14 indicated that the peptide encoded by SEQ ID NOs: 3, 83 and 85 was found on the cell membrane. As further evidence, Applicant submitted a declaration of Dr. Veltri in the Response to Office Action dated April 21, 2005, which is incorporated herein by reference. The declaration was made with respect to a co-pending application at that time but is believed to be relevant here as proof that UC 28 is expressed on the membrane of cancer cells. Declaration, ¶¶ 8, 9. Therefore, one of skill in the art would expect for an antibody that binds to a polypeptide encoded by SEQ ID NOs: 3, 83 and 85 to target cancer cells that overexpress these proteins.

The Examiner reasons that based on the following statement found on page 7017, col. 2 of An *et al.*, localization of UC 28 to the cell membrane must not have been remarkable: "UROC28 protein was localized primarily in the cytoplasm of prostate and breast cancer glandular epithelial cells." However, this statement does not make the distinction that the protein was in the cytoplasm *as opposed* to the membrane. It is perfectly consistent that the protein be in the cytoplasm but also membrane-bound—a point supported by the next statement in the An *et al.* reference, which refers to nuclear localization. Page 7017, col. 2.

Furthermore, Dr. Veltri identifies amino acids 34-50 of SEQ ID NO:2 of UC 28 as a putative transmembrane domain. Declaration, ¶ 6. As such, a portion(s) of UC 28 putatively is exposed to the cell surface. Dr. Veltri's statement is supported by the abstract of the An *et al.* reference, which states: "Bioinformation analyses suggest that there is a possible transmembrane domain from amino acids aa34 to aa50...." This statement is made in a peer-reviewed article in a scientific journal, and furthermore, it adds support to the argument that the authors of this

reference did not intend to distinguish cytoplasmic localization from membrane localization. Therefore, the basis for this ground of the rejection is without merit. The Examiner does not provide a reasonable basis for challenging the assertion in the specification that UC 28 localizes to the cell membrane, nor for challenging the assertion that at least a portion of UC 28 is expressed on the outside of the cell.

The Examiner tries to support the enablement rejection by asserting uncertainty with respect to this "putative" domain in combination with An *et al.*'s reference to UC 28's localization "primarily" in the cytoplasm. While the presence of the transmembrane is putative, Applicant notes that in examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d at 223-24. As discussed, localization of UC 28 "primarily" in the cytoplasm does not exclude its localization to the membrane. The presence of a putative transmembrane domain, in combination with Dr. Veltri's statement that UC 28 is localized to the cell membrane, together establish that UC 28 is localized to the cell membrane, thereby overcoming the enablement rejection.

c. The Specification Is Enabling For the Design of Chemotherapeutic Agents

With respect to claims 84 and 93, the Examiner asserts that the degree of unpredictability and extreme complexity in the art of anticancer drug discovery is such that a chemotherapeutic agent of the present invention cannot be recognized or made by routine experimentation alone. Applicant asserts that use of anticancer agents of the invention does not require undue experimentation. For example, in certain embodiments of the invention, binding agents may be conjugated to radionuclides or to chemotherapeutic agents. Use of radionuclides and

chemotherapeutic agents is well known in the art, and both radionuclides and chemotherapeutics are widely used in the treatment of cancer. Conjugation of radionuclides and/or chemotherapeutics to agents of the invention may increase their efficacy or reduce toxicity to healthy tissue. Thus, there would be no requirement for the kind of protracted analyses that the Examiner indicates would be necessary in order to practice the invention.

Moreover, as has been determined by the courts, the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *Fisher*, 427 F.2d at 839. Even if experiments are necessary, a considerable amount of routine experimentation is permissible; the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737 (Fed. Cir. 1985); *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 858 F.2d at 737 (citing *In re Angstadt*, 537 F.2d 489, 502-04 (CCPA 1976)). Thus, even if extensive experimentation is necessary to identify chemotherapeutic agents of the present invention, such experimentation does not mean the specification fails to enable the present claims.

In fact, binding antibodies that target cancer cells, such as those of the presently claimed invention, have been used in clinical trials. As described in the Response to Office Action dated April 21, 2005, incorporated herein, Carroll, 2004 reports use of a yttrium-90 labeled monoclonal antibody targets a membrane protein on prostate cancer cells. Results from this study indicated that the antibodies labeled with the radionuclide had "[a]cceptable toxicity, excellent targeting of known sites of PC metastases, and biologic activity" in patients. Thus, Carroll indicates that agents for the treatment of cancer such as those of the invention are known to be effective for

cancer therapy, and even for the treatment of solid tumors. As detailed above, the specification provides enabling written description that would allow a person of normal skill in the art to apply the invention for the treatment of cancer without undue experimentation.

d. The Specification Demonstrates a Correlation Between the Level of mRNA Expression and the Level of Protein Expression in Cancer Cells

The Examiner further indicates that the specification teaches that mRNAs corresponding to the sequences of the invention are overexpressed in cancer cells; however, the Examiner then states that it does not teach that the polypeptide encoded by these RNAs are overexpressed *per se* and therefore, a method for treating cancer by targeting cells overexpressing these polypeptides lacks enablement. Applicant respectfully traverses, because it is demonstrated in the specification that, for instance, UC 28 mRNA is overexpressed in breast cancer cells (FIG. 15), 4 out 5 bladder cancer cell lines (FIG. 16) and is hormone inducible in prostate in a prostate cancer cell line (FIG. 17). The Examiner concedes that the specification teaches overexpression in breast and prostate cancer cells. Action, page 21. Additionally, U.S. Patent Application Serial No. 08/692,787 (now U.S. Patent No. 5,886,284), incorporated by reference by the present specification at page 1, lines 6-8, describes the overexpression of UC 28 in prostate cells (*see, e.g.*, FIG. 3). While overexpression of the mRNAs in one cell line might result from random mutation during cancer development, overexpression in a wide range of cells would suggest to one of skill in the art that overexpression of the polypeptide was in fact advantageous to the cancer cell. Thus, the demonstration that a variety of cells overexpress the sequences of the invention implicitly indicates corresponding polypeptide overexpression.

Therefore, it is clear to one of skill in the art that the specification does teach that UC 28 protein is overexpressed in the cancer cells recited in the claims, thus enabling a method of treating cancer that targets cells expressing UC 28.

For the foregoing reasons, Applicant respectfully requests this rejection be withdrawn.

F. The Indefiniteness Rejection Is Overcome

The Examiner rejects claims 78-82, 86-91 and 94 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that the phrase "effective amount" is indefinite for allegedly failing to state the function that is to be achieved. More specifically, the Examiner states that it cannot be determined if the claim requires the "effective amount" of an agent to be sufficient to effectively inhibit the polypeptide, or to effectively treat cancer in a patient, or both. Applicant respectfully traverses.

As an initial matter, Applicant notes that in the Examiner's Answer mailed April 12, 2007, the Examiner withdrew this indefiniteness rejection. The following arguments are presented regardless of this withdrawal.

The standard of precision regarding indefiniteness is "whether one skilled in the art would understand the bounds of the claim when read in light of the specification.... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Miles Laboratory, Inc. v. Shandon Inc.*, 27 USPQ2d 112, 1126 (Fed. Cir. 1993). *See also Union Pacific Resources Co. v. Chesapeake Energy Corp.*, 57 USPQ2d 1293 (Fed. Cir. 2001) and MPEP § 2173.02. When read in light of the specification, the phrase "effective amount" is definite and satisfies all of the requirements of 35 U.S.C. § 112, second paragraph.

The phrase "effective amount" is found in independent claims 78 and 87, which recite: "A method of treating [a patient with breast cancer, bladder cancer or prostate cancer/a breast cancer, bladder cancer or prostate cancer cell] comprising administering to the [patient/cell] an effective amount of an agent that binds to a peptide or polypeptide encoded by...." As discussed above, Applicant notes that the claims do not recite the term "inhibit" with respect to administration of the claimed agents, but instead that "an effective amount of an agent that *binds to* a peptide or polypeptide" is administered (emphasis added). Thus, to the extent the Examiner's argument is based upon any required inhibitory activity of the claimed agents, the argument cannot support an indefiniteness rejection.

The meaning of the phrase "effective amount" is described in the specification: "An effective amount of the therapeutic composition is determined based on the intended goal." Specification, page 83, lines 29-30. It is clear to one of ordinary skill in the art that the goal of the rejected claims is to treat either: (a) a patient with breast cancer, bladder cancer or prostate cancer, or (b) a breast cancer, bladder cancer or prostate cancer cell, such that the amount of the agent administered binds to a peptide or polypeptide encoded by a claimed sequence. Accordingly, an "effective amount" of an administered agent is one that results in treatment of a patient or cell via binding to a peptide or polypeptide encoded by a claimed sequence. Therefore, this phrase is not indefinite, and one of ordinary skill in the art would understand the meaning and use of this phrase in the claims when read in light of the specification.

Further, one of ordinary skill in the art would be able to determine from the specification what an effective amount is. For example, page 83, line 29 through page 84, line 11, give guidance to a skilled artisan as to how to determine an effective amount, including exemplary unit dosages that may be administered. Such descriptive support renders the claims not

indefinite. *See, e.g., Ex part Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989) and MPEP § 2173.05(c).

The rejection of the phrase "effective amount" as being indefinite is therefore improper and should be withdrawn.

G. The Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejects claims 78-84 and 86-94 under the judicially created doctrine of obviousness type double patenting over claims 1-38 and 65-72 of Application No. 09/966,762. In response, Applicant notes that, if required, a terminal disclaimer over will be submitted upon an indication that the claims are otherwise allowable.

H. Conclusion

This is submitted to be a complete response to the referenced Office Action. In conclusion, Applicant submits that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned at (512) 536-3015 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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